Prevalence of Temporomandibular Disorders in Rheumatoid Arthritis and Associated Risk Factors: A Nationwide Study in Taiwan

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Aims: To investigate the association between temporomandibular disorders (TMD) and rheumatoid arthritis (RA), as well as potential risk factors for TMD and the preventive effect of medications on TMD, by using the Taiwan National Health Insurance Research Database. **Methods:** In total, 17,317 patients newly diagnosed with RA and 17,317 matched controls without RA were followed up from 2000 to 2010. Cox regression was used to determine risk factors for developing TMD. Kaplan-Meier curve with log-rank test was used to determine the cumulative risk of TMD in RA patients and the effects of antirheumatic medications. **Results:** Cox regression showed a higher risk of developing TMD if patients had RA (adjusted hazard ratio [HR] 2.538, $P < .001$) and a lower risk if patients were of male gender and elderly (≥ 40 years) in comparison to younger patients (20 to 29 years) ($P < .01$). Patients with insomnia, stroke, and mental disorders had, respectively, 4.756, 6.929, and 9.671 times the number of events of TMD compared to those without diseases ($P < .001$). No patients with RA treated with disease-modifying antirheumatic drugs (DMARDs) developed TMD after the 11-year follow-up. **Conclusion:** RA patients had 2.538 times the events of TMD compared with non-RA patients during this trial in Taiwan. The other risk factors for developing TMD included female gender, younger age, insomnia, stroke, and mental disorders. The DMARDs had a beneficial effect on prevention of TMD. *J Oral Facial Pain Headache 2017;31:e29–e36. doi: 10.11607/ofph.1917*

Keywords: *disease modifying anti-rheumatic drugs, methotrexate, National Health Insurance Research Database, rheumatoid arthritis, temporomandibular disorders*

Rheumatoid arthritis (RA), a chronic autoimmune disorder involving multiple joints and organs, can result in impaired quality of life (QoL) and even a shorter lifespan in more severe cases.[1] An RA-related systemic inflammatory response can cause joint inflammation, synovial cell proliferation and infiltration, erosion to the cartilage lining, and destruction of underlying bone in the early stages, as well as joint space narrowing, deformity, and dysfunction in later stages.[1] Small joints (eg, wrist, metacarpophalangeal joint, proximal interphalangeal joint, metatarsophalangeal joint) and medium to large joints (eg, shoulders, elbows, hips, knees, ankles, cervical spine) are commonly affected in a systemic and symmetric fashion. The temporomandibular joint (TMJ) may also be attacked in rheumatoid disease; however, it is the least-mentioned joint topic in RA.[2]

The TMJ is a synovial joint containing a temporal and mandibular articular surface, a fibrocartilage meniscus, and a well-lined synovial capsule.[1] Due to its synovial content, the TMJ is easily affected by RA. The prevalence of temporomandibular disorders (TMD) in patients with RA has been reported to be from 2% to 90.7%, and the most reported prevalence of TMJ involvement to be more than 50%.[1,3–9] This inconsistency could be attributed to diverse study designs, diagnostic criteria, sample sizes, and selection bias. Patients with TMD associated with RA usually report pain in the joint and masticatory muscles, joint sounds, and limited mouth opening[4]; thus, TMD may hamper overall functionality related to eating, tooth brushing, and pain, could decrease QoL, and could compromise the function of the stomatognathic or upper airway systems.[4]

Table 1 Diagnosis Groups with the Corresponding Codes of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)

ICD-9-CM	Diagnosis
714.0–714.2, 714.4	Rheumatoid arthritis
524.6	Temporomandibular disorders
800–804, 830, 941, 959.0	Any injuries on the head, face, or neck
088.81	Lyme disease
099.3	Reiter's disease
274	Gout
275.49	Other disorders of calcium metabolism (including pseudogout)
696	Psoriasis and similar disorders
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.2	Sicca syndrome
710.8	Other specified diffuse diseases of connective tissue
710.9	Unspecified diffuse diseases of connective tissue
714.3	Juvenile idiopathic polyarthritis
714.5	Osteoarthrosis, generalized
720	Ankylosing spondylitis and other inflammatory spondylopathies
	Comorbidities
250	Diabetes mellitus
401–405	Hypertension
296.2–296.3, 296.82, 300.4, 311	Depression
780.52	Insomnia
430–438	Stroke
290, 294.1, 331.0	Dementia
585	Chronic kidney disease
580–589	Nephritis, nephrotic syndrome, and nephrosis
244.9	Hypothyroidism
733.00–733.09	Osteoporosis
280	Anemia
272	Hyperlipidemia
345	Epilepsy
496	Chronic obstructive pulmonary disease
440.2–440.4, 440.8–440.9, 443, 444.2	Peripheral artery disease
410-414	Ischemic heart disease
290–319	**Mental disorders**
290–294	Organic psychotic conditions
295–299	Other psychoses
300–314	Neurotic disorders, personality disorders, and other nonpsychotic mental disorders
317–319	Intellectual disabilities

Therefore, early diagnosis and prompt management of TMD are necessary to reduce profound impairment of the TMJ in RA patients. To the authors' knowledge, there is still a lack of large population-based studies addressing RA-related TMD and its predictors. The only related study in Taiwan was small in sample size.[8] Thus, this study aimed to investigate the association between TMD and RA, as well as potential risk factors for TMD and the preventive effect of medications on TMD, by using the Taiwan National Health Insurance Research Database (NHIRD).

Materials and Methods

Study Design

The National Health Insurance (NHI) program has been established in Taiwan since March 1995 and has covered more than 99% of the 23 million people in the Taiwanese population until 2014.[10] The data used is a subset consisting of 1 million randomly selected subjects from the entire group of NHI program beneficiaries (approximately 23.75 million individuals in 2000). There is no significant difference between this subset and the original Taiwan NHIRD sample in the distribution of gender, age, and salary structure,[11,12] and its quality and validity have been claimed and verified in previous studies.[10,13] Hence, this reliable database was used to survey the prevalence of TMD in RA patients in the Taiwanese population and to investigate how comorbidities and drug therapy affected disease progression.

Diagnoses and comorbidities were identified by searching for the corresponding codes of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Table 1). Patients aged 16 years or older with a new diagnosis of RA or advanced disease related to RA who had been diagnosed twice during ambulatory visits or once for inpatient cases were identified from the Longitudinal Health Insurance Database (LHID) from 2000 to 2010 in Taiwan. Patients diagnosed as having RA before 2000 or TMD before tracking and those with unknown gender were not included. Patients with diseases that may involve the TMJ were excluded, including any sustained injuries on the head, face, or neck or having other rheumatoid and arthritis disease (eg, Lyme disease, Reiter's disease, gout, other disorders of calcium metabolism [including pseudogout], psoriasis and similar disorders, systemic lupus erythematosus, systemic sclerosis, sicca syndrome, other specified diffuse diseases of connective tissue, unspecified diffuse connective tissue disease, juvenile idiopathic polyarthritis [JIA], generalized osteoarthrosis, and ankylosing spondylitis and other inflammatory spondylopathies). The unique identifier of each patient ensured investigation of only the first diagnosis of each subject for multiple events. Controls without RA matched for gender, age, and index date were also enrolled for study. The study design was approved by the institutional review board, which exempted requirement for informed consent because of the de-identified patient data.

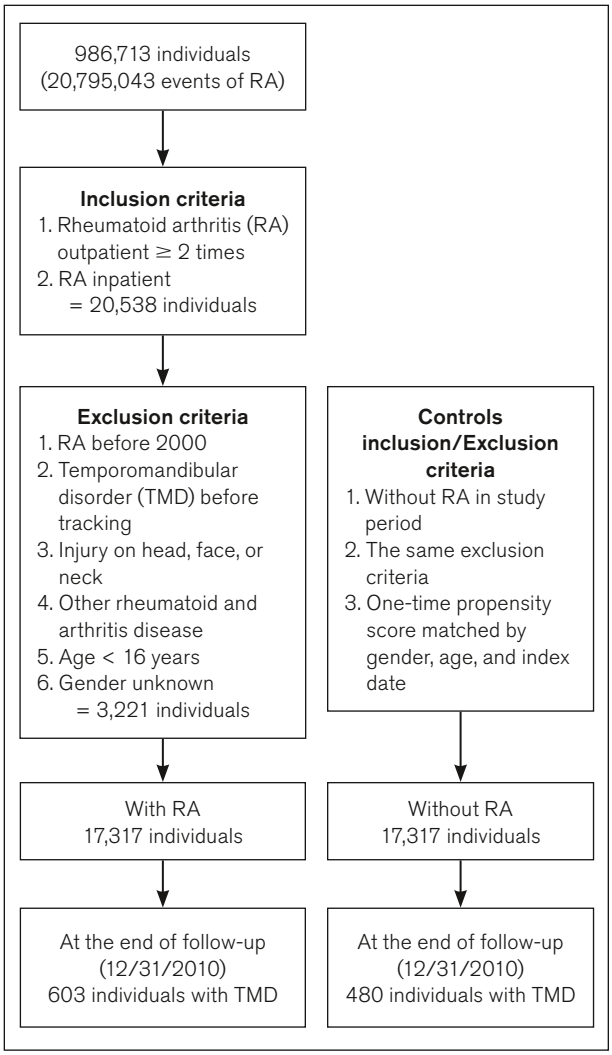

Fig 1 Flowchart of study sample selection from the National Health Insurance Research Database in Taiwan.

Table 2 Characteristics of Study Groups at Study Endpoint[a]

	With RA		Without RA		
Variables	n	%	n	%	*P*
Total	17,317	50.00	17,317	50.00	
TMD					< .001
Without	16,714	96.52	16,837	97.23	
With	603	3.48	480	2.77	
Insomnia					< .001
Without	17,269	99.72	17,303	99.92	
With	48	.28	14	.08	
Osteoporosis					.007
Without	17,261	99.68	17,285	99.82	
With	56	.32	32	.18	
Mental disorders					< .001
Without	16,756	96.76	16,899	97.59	
With	561	3.24	418	2.41	

RA = rheumatoid arthritis; TMD = temporomandibular disorders. [a]Chi-square test and Fisher exact test were used to examine the categorical variables at the endpoint. Categorical variables were as follows: gender; age group (16–19, 20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70 years); diabetes mellitus; hypertension; depression; insomnia; stroke; dementia; chronic kidney disease; nephritis, nephrotic syndrome, and nephrosis; hypothyroidism; osteoporosis; anemia; hyperlipidemia; epilepsy; chronic obstructive pulmonary disease; peripheral artery disease; ischemic heart disease; and mental disorders.

Statistical Analyses

SPSS software version 22 (SPSS) was used for all analyses in this study. Chi-square test and Fisher exact test were used to examine the categorical variables age group, gender, and comorbidity. Age was divided into subgroups (16–19, 20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70 years) for stratification.[14–16] The number of RA events for the 16–19 years age group was 0, and thus not included in the Cox regression analysis. Comorbidities included diabetes mellitus, hypertension, depression, insomnia, stroke, dementia, chronic kidney disease, nephritis, nephrotic syndrome/nephrosis, hypothyroidism, osteoporosis, anemia, hyperlipidemia, epilepsy, chronic obstructive pulmonary disease, peripheral artery disease, ischemic heart disease, and mental disorders. Cox regression for multivariate analysis was used to determine the adjusted hazard ratio (HR) with 95% confidence interval (CI). Kaplan-Meier method with log-rank test was used to determine the cumulative risk of TMD in RA and the therapeutic effect of potent medications, including systemic glucocorticoids (prednisolone and methylprednisolone) and disease-modifying antirheumatic drugs (DMARDs) (eg, methotrexate [MTX], sulfasalazine, hydroxychloroquine, leflunomide, etanercept, adalimumab, abatacept, rituximab, tocilizumab, and tofacitinib). A *P* value < .05 was considered statistically significant.

Results

From 2000 to 2010, 20,538 individuals with RA were enrolled, and 3,221 individuals were excluded. A total of 17,317 RA subjects and 17,317 matched controls were finally included (Fig 1). At baseline, gender and age were matched without intergroup differences. At the endpoint, significantly higher percentages of insomnia, osteoporosis, and mental disorders occurring in the RA group compared with the control group were noted. Significantly more TMD development in the RA group (3.48%) compared with the control group (2.77%) was also observed (Fig 1, Table 2).

As shown in Table 3, Cox regression analysis with variables adjusted showed a significantly higher event rate of TMD if patients had RA (adjusted HR 2.538) and a significantly lower event rate if they were male (adjusted HR F/M 1/0.644; equal to F/M 1.55/1) and older in comparison to the younger group (20–29 years): adjusted HR for 40–49 years = .609;

Table 3 Factors Affecting Event Rate of Temporomandibular Disorders at End of Follow-up Determined with Cox Regression[a]

Variables	Adjusted HR	95% CI Lower	95% CI Upper	*P*
RA				
Without	Reference			
With	2.538	2.240	2.876	< .001
Gender				
Male	.644	.556	.745	< .001
Female	Reference			
Age (y)				
20–29	Reference			
30–39	.689	.475	1.000	.050
40–49	.609	.427	.867	.006
50–59	.411	.289	.586	< .001
60–69	.348	.244	.497	< .001
≥ 70	.346	.242	.493	< .001
Insomnia[b]	4.756	2.496	9.064	< .001
Stroke[b]	6.929	2.653	18.099	< .001
Mental disorders[b]	9.671	5.649	16.555	< .001
Organic psychotic conditions[b]	9.672	5.594	15.736	< .001
Neurotic disorders, personality disorders, and other nonpsychotic mental disorders[b]	101.454	44.569	295.445	< .001

RA = rheumatoid arthritis; HR = hazard ratio; CI = confidence interval.
[a]Adjusted variables were listed as follows: gender; age group (20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70 years); rheumatoid arthritis; diabetes mellitus; hypertension; depression; insomnia; stroke; dementia; chronic kidney disease; nephritis, nephrotic syndrome, and nephrosis; hypothyroidism; osteoporosis; anemia; hyperlipidemia; epilepsy; chronic obstructive pulmonary disease; peripheral artery disease; ischemic heart disease; mental disorders. [b]Reference value: without.

Table 4 Kaplan-Meier Analysis for Cumulative Risk of Temporomandibular Disorder (TMD) Stratified by Rheumatoid Arthritis (RA) with Log-Rank Test

Years tracked	TMD (n) With RA (n = 17,317)	TMD (n) Without RA (n = 17,317)	*P*
1	99	24	.035
2	187	57	< .001
3	266	98	.001
4	332	131	< .001
5	399	180	< .001
6	460	236	< .001
7	502	295	< .001
8	546	347	< .001
9	578	384	< .001
10	595	431	< .001
11	603	480	< .001

for 50–59 years = .411; for 60–69 years = .348; and for ≥ 70 years = .346. The analysis also showed a significantly higher event rate of TMD in patients with insomnia, stroke, and mental disorders (4.756, 6.929, and 9.671 times, respectively) compared to those without diseases (Table 3). Subgroup analyses revealed that within mental disorders, organic psychotic conditions and neurotic disorders, personality disorders, and other nonpsychotic mental disorders were major contributors to the event of TMD. RA remained a significant risk factor for TMD after the Cox regression model was stratified by gender, age group, and comorbidity, except hypertension (P = .332) and stroke (P = .597) (data not shown).

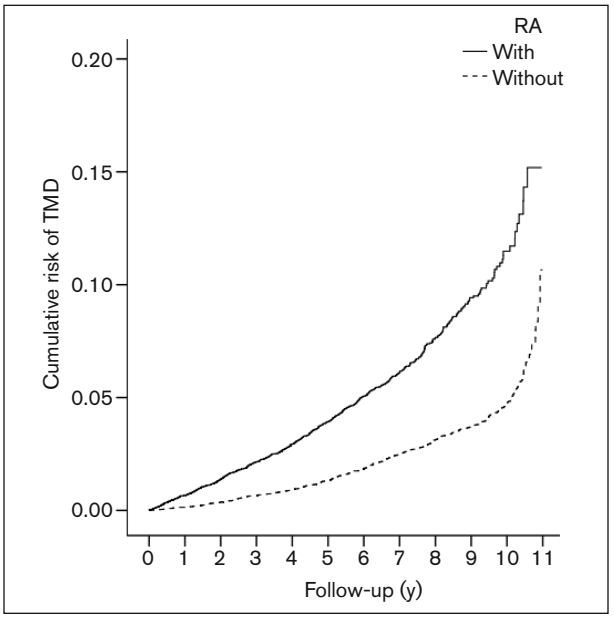

Fig 2 Kaplan-Meier analysis for cumulative risk of temporomandibular disorder (TMD) stratified by rheumatoid arthritis (RA) with log-rank test (log P < .001)

At the 11-year endpoint, Kaplan-Meier analysis for cumulative risk of TMD stratified by RA with log-rank test revealed a significantly higher incidence of TMD in the RA group (3.48%) than in the control group (2.77%) (Fig 2, Table 4). In the RA group, the cumulative risk of developing TMD was not significantly different between systemic glucocorticoids treatment (2.95%) and no drug treatment (log-rank P = .500) (data not shown). However, the cumulative risk of TMD in RA patients treated with DMARDs was 0 (Table 5).

Discussion

In the present study, RA was an independent risk factor for TMD (adjusted HR 2.538) regardless of age, gender, or comorbidity (except hypertension and stroke). Though systemic glucocorticoids seemed to

have no significant effect in reducing TMD in RA, patients with DMARD treatment were completely free of TMD after 11 years of follow-up. To the best of the authors' knowledge, the present research is the first large population-based study in this field. Moreover, it is the first to document that DMARDs significantly prevent TMD involvement in patients with RA.

In the present study, comorbidities such as insomnia, osteoporosis, and mental disorders showed a higher prevalence in the RA group. The findings are consistent with the literature in that RA as an independent risk factor for osteoporosis usually causes pain, disabilities, decreased QoL, and depression, which may further cause insomnia and other mental disorders.[2]

RA is an autoimmune disorder with multisystem involvement that mainly affects the synovium, so the TMJ may be vulnerable in this disease. Previous studies have reported the prevalence of TMD in RA to range widely—from 2% to 90.7%—with a rate of over 50% being most common.[1,3–9] The present study demonstrated an incidence of TMD of 3.48% in patients with RA and 2.77% in patients without RA. The incidence rate in this study is much lower compared with previous studies, but there are some possible explanations. First, the TMJ has a special drainage system in the retrodiscal space that facilitates drainage of effusion and alleviation of pain. Despite severe destruction of the TMJ, its function was not significantly limited in previous studies.[4,8] In addition, studies of patients with TMD show objective findings (ie, radiologic findings) more often than subjective findings.[6,8] Finally, TMJ symptoms were usually under-reported when masked by other joint complaints, such as those in weight-bearing joints or hand and finger joints, due to their daily heavy workload demands. Significant joint disabilities also hindered patients with RA-related TMD suffering from other joint complaints, such as weight-bearing joints, from visiting a doctor.[8] In contrast, previous studies recruited subjects by using subjective findings and physical examinations in addition to radiologic and histologic findings to intentionally explore the real prevalence of TMD even in clinically silent diseases. Therefore, the diagnosis of TMD may be under-registered in this nationwide population database.

In the present study, RA remained an independent risk factor for TMD after stratified by all variables except hypertension and stroke. The adjusted HR of 2.538 indicated that RA patients had 2.538 times the events of TMD compared with non-RA patients after adjusting for covariates at any time point during the trial.[17] The larger sample size and no selection bias of the present study compared with previous studies[1,3–9] has further documented the concept of RA as a risk factor for TMD.

Table 5 Kaplan-Meier Analysis for Cumulative Risk of Temporomandibular Disorder (TMD) Among Rheumatoid Arthritis (RA) Patients Stratified by Drug Therapy with Log-Rank Test

Drug name	No. of RA patients with drug therapy (n = 1,784)	Event (TMD) n	Event (TMD) %
Systemic glucocorticoids			
Prednisolone	1,727	51	2.95
Methylprednisolone	4	0	0
DMARDs			
Methotrexate	13	0	0
Sulfasalazine	33	0	0
Hydroxychloroquine	46	0	0
Leflunomide	0	0	0
Etanercept	0	0	0
Adalimumab	0	0	0
Abatacept	0	0	0
Rituximab	0	0	0
Tocilizumab	0	0	0
Tofacitinib	0	0	0

DMARDs = disease-modifying antirheumatic drugs.

Kaplan-Meier analysis showed that the RA group had a higher cumulative risk of TMD than the control group and also revealed significant intergroup differences beginning from very early stages. These differences became more and more significant after 2 years of follow-up, which is consistent with previous findings.[8,18] Tegelberg et al reported TMJ symptoms frequently occurred in the early stages of RA.[18] Moreover, Lin et al demonstrated that the majority of RA-related TMD patients developed symptoms before (18.5%) or shortly within 1 year (29.6%) of the involvement of other body joints.[8]

In the present study, younger age, female gender, and comorbidities such as stroke, insomnia, and mental disorders were independent risk factors for TMD. In the case of gender, females had 1.55 times the events of TMD compared to males. The finding of female predominance in TMD in this study is consistent with epidemiologic studies and may be ascribed to hormonal, behavioral, psychosocial, and constitutional characteristics.[19,20] Another study also documented that estrogen receptor-α polymorphisms predisposed women to a higher risk of TMD.[21] Other studies, however, have not found any correlation between gender and TMD, perhaps due to their small sample sizes.[3,8,22]

Higher rates of TMD in younger groups were noted, with trends gradually diminishing with age. This finding is different from those of other RA-related TMD studies[3–8]: Some concluded there was no significant correlation between age and TMD in RA patients,[3,7,8] and some did not address the correlation.[4–6] However, the current finding is supported by other

TMD studies conducted in general populations.[1,8,9,23] A meta-analysis by De Kanter et al showed that the highest percentage of TMD was in the general population aged 25 to 29 years, followed by 20 to 24 years, with a female predominance.[23] Broussard reported that the signs and symptoms of TMD decreased with age, and that the aged TMJ was less susceptible to inflammation-related cartilage damage. Nociceptive function may also decline with aging.[1] Moreover, Lin et al showed that the duration of active inflammation, rather than the total duration of RA, influenced the severity of TMD.[8] Finally, Garib et al demonstrated that a poorer periodontal condition began at a younger age in the RA group.[9] All of the above perspectives support the view that younger individuals may be predisposed to TMJ dysfunction and TMD because younger immune systems provide a more vigorous inflammatory response and more active disease status. Further research is needed to address this view.

Patients with insomnia, stroke, and mental disorders had 4.756, 6.929, and 9.671 times the events of TMD compared to those without diseases in the present study. Stroke patients usually have neurologic sequelae, including cognitive disturbance, facial palsy, dysphagia, and spasticity, which lead to uncoordinated orofacial movements and abnormal mandibular position, consequently resulting in TMJ dysfunction.[24] Another unusual case report depicted that antispasticity agents may predispose to post-stroke TMJ dislocation.[25] According to the above findings, it is possible that stroke patients are more prone to developing TMD.

There is, however, no convincing evidence that insomnia and mental disorders are predisposing factors for TMD. Nevertheless, Quartana et al have reported pain in TMD is associated with fluctuations of insomnia.[26] Lin et al have also noted that disc displacement disorders in TMD have a positive correlation with higher scores of depression, anxiety, insomnia, interpersonal hypersensitivity, and hostility.[27] Moayedi et al furthermore demonstrated the possible contribution of neuroticism to TMD through their finding of abnormal forebrain gray matter in their structural magnetic resonance imaging study.[28] Other mental disorders, including depression,[29–31] somatization,[30] higher distress, and personality disorder,[32] have been reported to affect the severity of TMD. Further research addressing psychological traits in TMD is needed.

In the case of pharmacologic therapy for RA, the present study showed there was no significant reduction in TMD risk in patients treated with systemic glucocorticoids. In contrast, those who had received DMARD therapy with either MTX, hydroxychloroquine, or sulfasalazine were completely free of TMD after 11 years of follow-up. There have been a few studies on the pharmacologic treatment of RA-related TMD.[33–35] Kopp et al reported that the combined use of MTX and infliximab (a tumor necrosis factor alpha [TNF-α] blocking agent) effectively reduced TMJ pain in RA patients by increasing anti-inflammatory cytokines and receptor levels in synovial fluid and serum[33]; however, the same authors also warned that high levels of serum interleukin-1β and positive rheumatoid factor will influence the potency of MTX combined with infliximab therapy for treating TMJ pain in RA.[34] Moen et al suggested that TNF-α blocking therapy in patients with RA showed long-term beneficial effects on the TMJ and general disease activity.[35] Cedströmer et al demonstrated that in JIA-related TMD, the severity of TMJ abnormalities was proportional to the use of any potent medication (eg, systemic corticosteroids, DMARDs, TNF-α inhibitor) at any time and the duration of medication treatment.[36] Arvidsson et al longitudinally evaluated 60 JIA children (mean age 8.6 years) with radiography and demonstrated that whether or not JIA patients were receiving MTX and/or biologic drugs, a large proportion (53%) showed TMD progression on average 27 years after baseline.[37] Twilt et al also stated that the use of corticosteroids and MTX in JIA should be recognized as a sign of disease severity, as their use contributed to a five-fold increase of TMD risk compared to no medication.[38] Stoll et al reported that children with JIA were exposed to a risk of TMJ arthritis even under concurrent immunosuppressive therapy.[39] On the other hand, Ince et al concluded that MTX therapy effectively reduced TMJ destruction and craniofacial dysmorphism in polyarticular JIA.[40] These varying findings may be ascribed to study design, disease type and status, inflammatory mediators, pharmacologic agents, and individual diversity in both the RA and JIA groups; however, based on the present findings and previous investigations,[33–35,40] it is suggested that DMARDs remain a beneficial agent in treating RA and preventing concurrent TMD. Further studies should be conducted to investigate the pharmacologic mechanisms and efficacy of DMARDs and newer TNF-α blocking agents for TMD.

There are several limitations of the present study. First, patients with RA and TMD could be identified by using the insurance claims data, but disease severity, laboratory parameters, radiologic and histologic changes, and medication adherence were not available. Second, the real prevalence of TMD in the Taiwanese population may be underestimated because quiescent cases of TMD may not be detected easily in usual clinical practice. Third, a longer follow-up period may be required to evaluate the therapeutic effects and adverse side effects of diverse agents. Finally, single or combination therapy and newer biologic immunomodulatory agents such as

TNF-α should be included in future studies. However, it is not likely that the aforementioned limitations interfered with the interpretation of the prevalence of clinically evident TMD in the RA group and the potential effect of medications most frequently used in Taiwan.

Conclusions

Patients in Taiwan with RA had 2.538 times the number of TMD events compared to those without RA during the course of this trial. In the long term, DMARDs, including MTX, had a beneficial effect on TMD prevention in patients with RA. Further studies are warranted to provide more details about the pharmacology, therapeutic efficacy, and long-term side effects of different drug therapies for RA combined with TMD.

Acknowledgments

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References

1. Broussard JS Jr. Derangement, osteoarthritis, and rheumatoid arthritis of the temporomandibular joint: Implications, diagnosis, and management. Dent Clin North Am 2005;49:327–342.
2. Erickson AR, Cannella AC, Mikuls TR. Clinical features of rheumatoid arthritis. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR (eds). Kelley and Firestein's Textbook of Rheumatology, ed 10. Philadelphia: Elsevier, 2017:1167–1186.
3. Aceves-Avila FJ, Chávez-López M, Chavira-González JR, Ramos-Remus C. Temporomandibular joint dysfunction in various rheumatic diseases. Reumatismo 2013;65:126–130.
4. Aliko A, Ciancaglini R, Alushi A, Tafaj A, Ruci D. Temporomandibular joint involvement in rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis. Int J Oral Maxillofac Surg 2011;40:704–709.
5. Gynther GW, Holmlund AB, Reinholt FP, Lindblad S. Temporomandibular joint involvement in generalized osteoarthritis and rheumatoid arthritis: A clinical, arthroscopic, histologic, and immunohistochemical study. Int J Oral Maxillofac Surg 1997;26:10–16.
6. Helenius LM, Hallikainen D, Helenius I, et al. Clinical and radiographic findings of the temporomandibular joint in patients with various rheumatic diseases. A case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:455–463.
7. Kurtoglu C, Kurkcu M, Sertdemir Y, Ozbek S, Gürbüz CC. Temporomandibular disorders in patients with rheumatoid arthritis: A clinical study. Niger J Clin Pract 2016;19:715–720.
8. Lin YC, Hsu ML, Yang JS, Liang TH, Chou SL, Lin HY. Temporomandibular joint disorders in patients with rheumatoid arthritis. J Chin Med Assoc 2007;70:527–534.
9. Garib BT, Qaradaxi SS. Temporomandibular joint problems and periodontal condition in rheumatoid arthritis patients in relation to their rheumatologic status. J Oral Maxillofac Surg 2011;69:2971–2978.
10. Shih CJ, Chu H, Chao PW, et al. Long-term clinical outcome of major adverse cardiac events in survivors of infective endocarditis: A nationwide population-based study. Circulation 2014;130:1684–1691.
11. Yang K, Jung SJ, Lee H, Choi IJ, Lee JH. Topographical relations between the Gantzer's muscle and neurovascular structures. Surg Radiol Anat 2017. Epub ahead of print.
12. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: A population-based follow-up study. Stroke 2009;40:3443–3448.
13. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–242.
14. Keller JJ, Chung SD, Lin HC. A nationwide population-based study on the association between chronic periodontitis and erectile dysfunction. J Clin Periodontol 2012;39:507–512.
15. Tzeng NS, Chung CH, Yeh CB, et al. Are chronic periodontitis and gingivitis associated with dementia? A nationwide, retrospective, matched-cohort study in Taiwan. Neuroepidemiology 2016;47:82–93.
16. Chin CY, Weng MY, Lin TC, Cheng SY, Yang YH, Tseng VS. Mining disease risk patterns from nationwide clinical databases for the assessment of early rheumatoid arthritis risk. PLoS One 2015;10:e0122508.
17. Barraclough H, Simms L, Govindan R. Biostatistics primer: What a clinician ought to know: Hazard ratios. J Thorac Oncol 2011;6:978–982.
18. Tegelberg A, Kopp S. Subjective symptoms from the stomatognathic system in individuals with rheumatoid arthritis and osteoarthrosis. Swed Dent J 1987;11:11–22.
19. Bagis B, Ayaz EA, Turgut S, Durkan R, Özcan M. Gender difference in prevalence of signs and symptoms of temporomandibular joint disorders: A retrospective study on 243 consecutive patients. Int J Med Sci 2012;9:539–544.
20. Poveda Roda R, Bagan JV, Díaz Fernández JM, Hernández Bazán S, Jiménez Soriano Y. Review of temporomandibular joint pathology. Part I: Classification, epidemiology and risk factors. Med Oral Patol Oral Cir Bucal 2007;12:e292–e298.
21. Ribeiro-Dasilva MC, Peres Line SR, Leme Godoy dos Santos MC, et al. Estrogen receptor-alpha polymorphisms and predisposition to TMJ disorder. J Pain 2009;10:527–533.
22. Magalhães BG, de-Sousa ST, de Mello VV, et al. Risk factors for temporomandibular disorder: Binary logistic regression analysis. Med Oral Patol Oral Cir Bucal 2014;19:e232–e236.
23. De Kanter RJ, Truin GJ, Burgersdijk RC, et al. Prevalence in the Dutch adult population and a meta-analysis of signs and symptoms of temporomandibular disorder. J Dent Res 1993;72:1509–1518.
24. Oh DW, Kang TW, Kim SJ. Effect of stomatognathic alignment exercise on temporomandibular joint function and swallowing function of stroke patients with limited mouth opening. J Phys Ther Sci 2013;25:1325–1329.
25. Wright AJ. An unusual but easily treatable cause of dysphagia and dysarthria complicating stroke. Br Med J (Clin Res Ed) 1985;291:1412–1413.
26. Quartana PJ, Wickwire EM, Klick B, Grace E, Smith MT. Naturalistic changes in insomnia symptoms and pain in temporomandibular joint disorder: A cross-lagged panel analysis. Pain 2010;149:325–331.

27. Lin SL, Wu SL, Huang HT, Lung FW, Chi TC, Yang JW. Can a 10-minute questionnaire identify significant psychological issues in patients with temporomandibular joint disease? J Oral Maxillofac Surg 2017;75:1856–1865.
28. Moayedi M, Weissman-Fogel I, Crawley AP, et al. Contribution of chronic pain and neuroticism to abnormal forebrain gray matter in patients with temporomandibular disorder. Neuroimage 2011;55:277–286.
29. Auerbach SM, Laskin DM, Frantsve LM, Orr T. Depression, pain, exposure to stressful life events, and long-term outcomes in temporomandibular disorder patients. J Oral Maxillofac Surg 2001; 59:628–633.
30. Dworkin SF, Sherman J, Mancl L, Ohrbach R, LeResche L, Truelove E. Reliability, validity, and clinical utility of the Research Diagnostic Criteria for Temporomandibular Disorders Axis II Scales: Depression, non-specific physical symptoms, and graded chronic pain. J Orofac Pain 2002;16:207–220.
31. Manfredini D, di Poggio AB, Romagnoli M, Dell'Osso L, Bosco M. Mood spectrum in patients with different painful temporomandibular disorders. Cranio 2004;22:234–240.
32. Ferrando M, Andreu Y, Galdón MJ, Durá E, Poveda R, Bagán JV. Psychological variables and temporomandibular disorders: Distress, coping, and personality. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:153–160.
33. Kopp S, Alstergren P, Ernestam S, Nordahl S, Morin P, Bratt J. Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs 2005;180:22–30.
34. Kopp S, Alstergren P, Ernestam S, Nordahl S, Bratt J. Interleukin-1beta influences the effect of infliximab on temporomandibular joint pain in rheumatoid arthritis. Scand J Rheumatol 2006;35:182–188.
35. Moen K, Kvalvik AG, Hellem S, Jonsson R, Brun JG. The long-term effect of anti TNF-alpha treatment on temporomandibular joints, oral mucosa, and salivary flow in patients with active rheumatoid arthritis: A pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:433–440.
36. Cedströmer AL, Ahlqwist M, Andlin-Sobocki A, Berntson L, Hedenberg-Magnusson B, Dahlström L. Temporomandibular condylar alterations in juvenile idiopathic arthritis most common in longitudinally severe disease despite medical treatment. Pediatr Rheumatol Online J 2014;12:43.
37. Arvidsson LZ, Flatø B, Larheim TA. Radiographic TMJ abnormalities in patients with juvenile idiopathic arthritis followed for 27 years. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:114–123.
38. Twilt M, Mobers SM, Arends LR, ten Cate R, van Suijlekom-Smit L. Temporomandibular involvement in juvenile idiopathic arthritis. J Rheumatol 2004;31:1418–1422.
39. Stoll ML, Sharpe T, Beukelman T, Good J, Young D, Cron RQ. Risk factors for temporomandibular joint arthritis in children with juvenile idiopathic arthritis. J Rheumatol 2012;39:1880–1887.
40. Ince DO, Ince A, Moore TL. Effect of methotrexate on the temporomandibular joint and facial morphology in juvenile rheumatoid arthritis patients. Am J Orthod Dentofacial Orthop 2000; 118:75–83.